REMARKS

Applicant has amended claims 10-12, 23-26, and 33-36 as detailed in the marked up set of claims, as a result, claims 1-38 are now pending.

ISSUES UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 32 and 37 under 35 U.S.C. § 112, first paragraph one, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art as to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner asserts that the specification does not provide working *in vivo* examples to support the implied *in vivo* application of the claims and furthermore states that claims 32 and 37 are beyond the scope of one of ordinary skill in the art because of "the amount of experimentation necessary to determine the appropriate mode of delivery of the suppressor tRNA gene sequence into an animal" and perceived problems with potential toxic side effects and mode of delivery. These rejections are respectfully traversed.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), which posited the question whether the experimentation needed to practice the invention was undue or unreasonable. Relevant factors were outlined by the Court of Federal Appeals for the Federal Circuit in *In re Wands*, 858 F.2d 731, 8U.S.P.Q.2d 1400 (Fed. Cir. 1988). These factors include: (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples relating to the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of claims.

The determination of undue experimentation needed to practice the claim is not a single, simple factual determination. Rather, it is determined by weighing the all factual considerations, including the eight identified above. *In re Wands*, 8U.S.P.Q.2d at 1404.

Analysis of the factors in *In re Wands* shows that it would not be undue experimentation to practice the present invention as claimed. (1) *The quantity of experimentation necessary.* When analyzing whether it requires "undue experimentation" to practice claimed methods, the emphasis is on "undue" not "experimentation." *In re Angstadt*, 190 U.S.P.Q. 214, 219 (CCPA 1976). Enablement is not precluded by the necessity for some experimentation, such as (increasing efficiency for) delivery of vectors *in vivo* gene delivery. In fact, a considerable amount of experimentation is permissible if it is routine or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Furthermore, the Examiner stated in the Office Action that a gene therapy delivery system "depends upon the successful development of vectors that can deliver the ... gene more efficiently to allow for a sustainable gene expression" (page 2 of the Office Action). It is respectfully submitted that Examiner refers to one sentence taken out of Li's entire article, and fails to note that the reference as a whole shows that even low efficiency of the tRNA suppressor rescues gene expression *in vivo*. (page PL207-08). It is respectfully submitted that the delivery system is not required to be optimal and, therefore, does not constitute "undue experimentation," especially in an art where the skill level is high. *In re Wands*, 8 U.S.P.Q. at 1404.

(2) *The amount of direction or guidance presented.* Applicant's specification provides sufficient guidance to allow one of skill in the art to practice the claimed invention. To take some examples, the preparation of several viral vectors, including Moloney Murine Leukemia

Virus, Herpes Virus are incorporated through references taught on pages 5-8 and in Examples on page 11. Furthermore, one skilled in the art, if necessary, can properly look to the state of the art gene delivery protocols for useful guidance with respect to increasing the efficacy of delivery *in vivo*. For example, *see* Li (incorporated through reference, at pages 4-5 of the specification). *See also* VandenDriessche et al., *Viral vector-mediated gene therapy for hemophilia*, CURR GENE THER,, 1(3), 301-15, (2001) (noting that "Significant progress has been made recently in the development of gene therapy for hemophilia. This has been primarily due to the technical improvements of existing vector systems and the development of new gene delivery methods. Therapeutic and sometimes physiologic levels of FVIII and FIX could be achieved in FVIII- and FIX-deficient mice and hemophilic dogs using different types of viral vectors"). Therefore, Applicant has provided ample disclosure, with respect to a method for effective *in vivo* gene delivery, to enable one skilled in the art to practice the invention as claimed. Thus, Applicant respectfully submits that the disclosure, coupled with knowledge in the art at the time the application was filed, would adequately enable one of skill in the art to deliver a tRNA suppressor gene *in vivo*.

(3) *The presence or absence of working examples relating to the invention.* The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. M.PE.P. § 2164.02. Additionally, an *in vitro* example in the specification, in effect, constitutes a "working example" if that example correlates with a disclosed or claimed method invention. M.P.E.P. § 2164.02. At page 3, of the specification, an *in vitro* model is disclosed. In figures 5 and 6, described at page 3, data is presented that shows that the representative vectors expressing suppressor tRNA in the human Xeroderma pigmentosum cell

line XP12ROSV possess efficacy for correcting a DNA repair deficient phenotype. Additionally, figure 8, described at page 3, of the specification, data is presented that shows that the tRNA vectors successfully transduced XP12ROSV cells using the herpes amplicon system which resulted in suppression of a gene containing a nonsense mutation. The Applicant respectfully submits that the instant specification contains *in vitro* models which constitute working examples that clearly support the recited utility of the claimed *in vivo* method. M.P.E.P. § 2164.02.

(4) *The nature of the invention.* The nature of the invention is tRNA suppressor genes and methods of delivery of these genes. Gene delivery and regulation of gene expression has been known for many years and a variety of gene regulation methods are available. *See* W. Walther & U. Stein, *Viral Vectors For Gene Transfer: a Review of Their Use in the Treatment of Human Diseases,* DRUGS, 60(2), 249-71 (2000). M.G. Peterson & V. R. Baichwal, *Transcription Factor Based Therapeutics: Drugs of the future?*, TRENDS BIOTECHNOL, 11(1):11-8, (1993), *see also* N. Dillon, *Regulating Gene Expression in Gene Therapy*, TRENDS BIOTECHNOL, 11(5), 167-73 (1993). Furthermore, the U.S. Patent and Trademark Office has recognized the patentability of methods for *in vivo* gene delivery, see for example U.S. Patent Nos. 5,661,033, Gene transfer using herpes virus vectors as a tool for neuroprotection, or 5,869,037, Adenoviral-mediated gene transfer to adipocytes. Thus, the instant invention falls within the gene delivery field.

(5) *The state of the prior art.* Neither gene delivery nor regulation of gene expression is a new field. For over a decade, methods for both gene delivery and gene regulation have been available, including the use of viral vectors, naked DNA transfer, electroporation, lipsomes, or *ex vivo* transfer methods. As an example, a gene of interest may be introduced simply to replace a defective gene or to suppress growth of tumor cells. Currently, there are a number of gene

delivery methods that have been successfully used to regulate gene expression in an *in vivo* setting. For examples, *see supra* VandenDriessche and Li (pages 4-5 of the specification).

(6) *The relative skill of those in the art.* The relative skill of one in the art is high. Generally, one considered of skill in the art for the instant invention will have an advanced degree, either an M.D. or Ph.D. or both.

(7) *The predictability or unpredictability of the art.* The Examiner states that the outcome of the *in vivo* delivery of tRNA suppressor genes is unpredictable, specifically the Examiner cites the concern of toxicity, pages 2-3 of the Office Action. It is respectfully submitted that Examiner bases this supposition on one or two sentences taken out of Li's entire article, rather than acknowledge that Li's data shows that suppressor tRNA transfer works *in vivo*. (page PL205). "This is the first convincing data that a tRNA suppressor gene might be a useful *in vivo* treatment for the genetic disorders caused by nonsense mutations." (page PL205). Furthermore, at page PL208, Li states that the concern that the suppressor tRNA might cause potential read-through of other genes "may not be important" (page PL208). Similar to Li, the Applicant did not observe any significant toxicity to the cells when performing the *in vitro* studies, page 3. One skilled in the arts could ameliorate the side effects of toxicity if necessary through routine experimentation by tweaking the protocol, i.e. lowering the dose of suppressor tRNA and administering suppressor tRNA over longer periods of time. The fact that random (non-specifically targeted) genes may be affected by the gene transfer and cause toxicity/apoptosis are *possible* consequences and not dispositive that these results will occur. *See* Li. Additionally, other scientists have not observed adverse effects in animals after gene transfers were performed. (*See,* H.C. Lee et al, *Remission in Models of Type 1 Diabetes by Gene Therapy Using a Single-Chain Insulin Analogue*, NATURE, 408(6811), 483-88 (2000) (noting that the scientists used a

recombinant adeno-associated virus to deliver an insulin analogue to streptozotocin-induced diabetic rats and autoimmune diabetic mice without any apparent side effects.).

Antisense oligonucleotides, short, single-stranded DNA that hybridize to specific mRNA sequences and inhibit synthesis of a protein, have practically the same potential to cause havoc with regards to targeting non-specific mRNAs as the instant invention since the introduced sequences may contain a sequence common to other mRNAs and result in non-specific hybridization. Some studies have shown that viral vector-mediated gene transfer of antisense oligonucleotides, however, does not have adverse effects. *See* Phillips et al, *The Potential Role of Antisense Oligodeoxynucleotide Therapy For Cardiovascular Disease*, DRUGS, 60(2), 239-48 (2000) (showing no adverse effects in neither rats nor transgenic mice from the use of a viral vector delivery of antisense oligonucleotides to inhibit genes associated with vasoconstrictive properties).

Furthermore, the fact that an art worker may have to investigate toxicity or other by-products of the transfer to determine whether the gene delivery was effective, e.g., that is effectively suppressed the expression of an individual gene, is not noteworthy, particularly in an art area in which the level of skill is very high and in which assaying for toxicity has been the standard practice for years, does not constitute "undue experimentation." Ex *parte Forman*, 230 U.S.P.Q. 546 (Bd. App. 1986).

(8) *The breadth of claims*. Claim breadth alone does not provide the basis for a nonenablement rejection. *In re Moore*, 169 U.S.P.S. 236 (C.C.P.A. 1971). The scope of enablement provided by Applicant need only bear a "reasonable correlation" to the scope of the claims. *In re Fischer*, 166 U.S.P.S. 18, 24 (C.C.P.A. 1970). Methods for making and cloning synthetic tRNA suppressor gene oligonucleotides into vector constructs are disclosed and their

use for gene delivery is adequately described, see specification at page 9. Furthermore, Applicant submits that the claims are not overly broad. Claims 32 and 37 recite a tRNA suppressor gene method for treating an animal *in vivo*. Again, as under factor 2, the amount of direction or guidance presented, an art worker, if necessary, can properly look to the state of the art gene delivery protocols for useful guidance with respect to increasing the efficacy of delivery *in vivo*. Thus, Applicant respectfully submits that the scope of enablement provided by the Applicant's specification is sufficient for breadth of the instant claims.

The first paragraph of 35 U.S.C. § 112 requires no more than a disclosure sufficient to enable on skilled in the art to carry out the invention commensurate with the scope of the claim. The above evaluation of the factual considerations outlined by the court in *In re Wands* demonstrate that the claimed invention can be practiced without undue or unreasonable experimentation. Thus, the Applicant respectfully submits that the instant application complies with 35 U.S.C. § 112, first paragraph.

Furthermore, the Examiner has not provided any factual evidence to suggest that the instant specification fails to provide adequate guidelines to enable one skilled in the art to practice the claimed invention. Thus, the Examiner has failed to meet the initial burden required to establish a rejection of the instant claims under § 112. Claims 32 and 37 recite a method for delivery of tRNA suppressor genes to animals. The specification provides examples of how it can be practiced *in vitro*. The specification further provides information regarding the administration of the instant method *in vivo* that would enable one skilled in the art to practice the claimed method *in vivo* without undue experimentation (*See* Li, at page 4-5).

Additionally, it is not the function of the claims to exclude all possibly inoperable embodiments. *In re Anderson*, 471 F.2d 1237, 176 U.S.P.Q. 331 (C.C.P.A. 1973); *Atlas Powder*

Co. v. E. I. Du Pont De Nemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984). Rather, it is the specification which must be evaluated to determine whether or not the specification would enable the art worker to practice the invention without undue experimentation. *Ex parte Forman*, 230 U.S.P.Q. 546 (B.P.A.I. 1986). As discussed above, the specification provides adequate guidance to one of skill in the art to deliver tRNA suppressor genes *in vivo*. Therefore, Applicant's specification meets the enabling requirement of 35 U.S.C. § 112, paragraph one.

REJECTION OF CLAIM 19

The Examiner rejected claim 19 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art as to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner asserts the specification does not provide a repeatable method for making pHhargsuptRNAOpal vector and therefore the vector should be deposited for compliance with enablement requirements under 35 U.S.C. § 112, first paragraph. Applicant respectfully traverses this rejection.

M.P.E.P § 608.01(p) states that some inventions, which are the subject of patent applications, depend on the use of microorganisms that must be described in the specification in accordance with 35 U.S.C. § 112. No problem exists when microorganisms used that are known and readily available to the public. Analogously, when a necessary biologic material can be readily prepared from materials which are publicly available, section 112 is satisfied by the identification of the source of the necessary starting materials, and a description of the method of making the invention based upon starting materials sufficient that one skilled in the art can make and use the invention. Tubuchi v. Nubel, 559 F.2d 1183 (C.C.P.A. 1977).

The Federal Circuit has similarly decided that the deposits need not be made if the material of interest "can be made or isolated without undue experimentation." Amgen v. Chugai Pharmaceuticals, 927 F.2d 1200 (Fed. Cir. 1991), cert. denied, 112 S.Ct. 169 (1991). The pHhargsuptRNAOpal vector its construction is explicitly described in the specification at page 9. The description is also supplemented by several journal articles which were incorporated by reference, including Wang et al., *A Novel Herpes Virus Amplicon System for In Vivo Gene Therapy*, GENE. THER. 4, 1132-1141 (1997). In addition the expression vector is disclosed in Figure 2B in great detail. Thus the publicly available Herpes virus vector amplicon system is modified as described in the specification to include an insert of the opal suppressor tRNA. As such, it would not require undue experimentation to obtain the vector of interest, as all starting materials are provided and a description for the construction of the vector is provided in great detail in the specification.

In light of the remarks above, the present application has clearly described an enabled the claimed invention and, therefore, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 19, 32, and 37 under 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 7, 12, and 26 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. Claims 7, 12 and 26 have been amended and Applicant believes that the claim is allowable under 35 U.S.C. 112, first paragraph and requests that rejections be withdrawn.

ISSUES UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 10-12, 23-26, 33-36 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner has indicated that claims 10-12, 23-26, and 33-36 are vague and indefinite since it is unclear if these claims are drawn specifically to an oligonucleotide or to a method. Applicant thanks Examiner for this observation and Applicant has amended claims 10-12, 23-26, 33-36 to provide the necessary antecedent basis. In claims 10-11, 23-25, 33-35 the word "oligonucleotide" has been amended to "method."

Therefore, in view of the amendments made to claims 10-11, 23-25, 33-35, Applicant believes that the claim is allowable under 35 U.S.C. 112, second paragraph. Accordingly, withdrawal of the rejections is requested.

ISSUES UNDER 35 U.S.C. § 103

Claims 1-6, 8-11, 13-15, 16-22, 24-25, and 38-39 were rejected under 35 U.S.C. 103(a) as being unpatentable under Sharp et al, Temple et al, Li et al, Noren et al, and Atkinson et al. The Examiner rejected the following three independent claims: claim 1, claim 8, and claim 22. Applicants respectfully traverse this rejection.

Applicant continues to assert that that Examiner has not established a prima facie case of obviousness. The Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). To do that the Examiner must show that some objective teaching in the prior art or some knowledge generally available to one of ordinary skill in the art would lead an individual to combine the relevant teaching of the references. *Id.* The M.P.E.P. adopts this line of reasoning, stating that

> In order for the Examiner to establish a *prima facie* case of obviousness, three base criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *M.P.E.P.* § 2142 (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).

Applicant respectfully asserts that the Examiner has not met all three requirements for the pending claims. Applicant respectfully submits that the Office Action did not make out a *prima facie* case of obviousness.

The reference (or references when combined) must teach or suggest all the claim elements. M.P.E.P. § 2142 (citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)).The Federal Circuit has clearly established the analytical framework for the § 103(a) obviousness inquiry.

> A proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). Further, "both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." In re Dow Chemical Co., 837 F.2d 469 (Fed. Cir. 1988). Finally, "it is impermissible to use the claimed invention as an instruction manual or a 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." In re Fritch, 972 F.2d 1260 (Fed. Cir. 1992).

Examiner asserts that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing of the instant application to design oligonucleotides encoding human

suppressor tRNAs of less than 500bp and to design methods of use of said human suppressor tRNAs embraced by the claimed invention." Examiner correctly points out that Atkinson et. al. teaches that "the length of an active transcription unit may be considerably less than 500 base pairs, and thus accommodation within a delivery vector presents no problem." Atkinson's journal article in its entirety does not study the length of an active tRNA transcription unit, rather, in contrast to claim 1 as an example, describes the effect that the codon that is 3' to nonsense codons has on tRNA suppressor efficiency. (Page 1328-1330). Examiner also correctly points out that Sharp et al. and Noren et al. teach methods for creating tRNA-coding oligonucleotides in which the anticodon has been altered. However, the method taught by each of these references is based on the traditional method where tRNA molecules are laboriously isolated, cloned and finally site-mutated to alter the anticodon. The present invention departs significantly from the traditional method, and the incarnations described by Sharp et al. and Noren et al. The present invention describes a novel two-step method that involves designing an oligonucleotide containing only the tRNA structural sequence and less than 20 3' flanking nucleotides that incorporates the desired alteration of the anti-codon, followed by routine synthesis of the vector-ready oligonucleotide. This design and synthesis approach is far more time and resource efficient than the traditional isolation, cloning, and site-directed mutagenesis approach, and allows the construction of tRNA-coding oligonucleotides of about 100 base pairs in length. Notably, the vector-ready oligonucleotides are up to 5 times shorter than appreciated by Atkinson et al.; a feature that facilitates cloning and even allows the potential to incorporate multiple (e.g., tandem) copies of the tRNA-coding oligonucleotide in the vector. Finally, the Examiner notes that "Temple et al. disclose a functional human lysine tRNA (containing an anticodon which recognizes the amber termination codon UAG) gene whose length is approximately 76 base

pairs, this gene was subcloned into M13mp7 phage." Examiner failed to note that Temple et al's strategy to clone a tRNA fragment differs from the instant invention in that Temple employs a subcloned tRNA gene fragment that is 800bp in length, whereas the instant invention strategy involves synthesizing tRNA sequence that is less than 100 bp in length.

The references cited by the Examiner do not render the present invention obvious, as they do not satisfy the first requirement for obviousness, as set forth in In re Vaeck. The cited references do not individually or collectively teach or suggest that one of ordinary skill in the art should carry out the invention as claimed. Furthermore, the cited references do not teach or suggest the novel two-step design and synthesis method for constructing synthetic tRNA-coding oligonucleotides described by in dependent claim 4. Further, the cited references do not individually or collectively teach or suggest making or using synthetic tRNA-coding oligonucleotides having the features inhered by the novel design and synthesis method. Each of the claims against which the Examiner raises a § 103(a) objection is unreachably distant from the teachings and suggestions of the prior art by the incorporation of synthetic tRNA-coding oligonucleotides having the features inhered by the novel design and synthesis method.

It respectfully submitted that the Examiner appears to be employing hindsight to arrive at the Applicant's invention, selecting aspects from four different references to attempt to piece together Applicant's invention, especially in the absence of any suggestion in the cited art to take Applicant's approach. The Examiner is reminded that it is impermissible to use the Applicant's specification as a template to arrive at the conclusion that the claimed invention is obvious. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Fritisch*, 23 USPQ2d 1780, 1782 (Fed. Cir. 1992). To render the invention obvious, the combination of the

cited art must teach or suggest the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). None of these references, either alone or taken in combination, teach the present claimed invention.

Claims 2-6 are dependent on claim 1. Claims 2-6 are likewise nonobvious as dependent on claim 1 which is nonobvious.

The method of claim 8 is method of restoring translation to a nucleotide sequence which includes a nonsense mutation in a cell by introducing to the cell a synthetic suppressor tRNA oligonucleotide which is encoded by the sequence of claim 1. Like claim 8, the sequence is nonobvious, and, therefore, the method of introducing the sequence is nonobvious based on the cited references. Claims 9-11 are dependent on claim 8 and, therefore, also nonobvious.

The method of claim 13 is method of restoring translation to a nucleotide sequence which includes a nonsense mutation in a cell by introducing to the cell a synthetic suppressor tRNA oligonucleotide which is encoded by the sequence of claim 1. Like claim 8, the sequence is nonobvious, and, therefore, the method of introducing the sequence is nonobvious based on the cited references. Claims 14-15 are dependent on claim 8 and, therefore, also nonobvious.

Claim 14 is a nucleotide vector comprising the nucleotide sequence of claim 1. Since the claim 1 sequence is nonobvious based on the cited references, claim 14 is likewise nonobvious. Claims 16-19 are dependent on claim 14 and, therefore, also nonobvious. Claim 20 is a transformed host cell comprising the sequence of claim 1. Since the sequence of claim 1 is nonobvious, claim 20 does not become obvious by virtue of transforming a host cell with it. Claim 20 is nonobvious. Claim 21 is a transformed host cell comprising the synthetic suppressor tRNA molecule of claim 2. Claim 2 is nonobvious as dependent on claim 1 which is nonobvious. Since a synthetic suppressor tRNA molecule encoded by the oligonucleotide of

claim 1sequence of claim 2 is nonobvious, claim 21 does not become obvious by virtue of transforming a host cell with it. Claim 21 is nonobvious.

Claim 22 is a method for introducing a site-specific mutation to a nonsense mutated protein which includes introducing to a cell a sequence as defined in claim 1. The sequence of claim 1 is nonobvious, so a method of introducing the nonobvious sequence is also nonobvious. Claims 23-25 are dependent on claim 22 and, therefore, are nonobvious.

Claim 38 is a method of monitoring transduction of cells including the step of introducing to cells the sequence of claim 1. The sequence of claim 1 in nonobvious in view of the cited references, and, therefore, this claim must be as well. Claim 39, which depends from claim 38, also includes the step of introducing the nonobvious sequence, so is nonobvious.

Therefore, Applicant respectfully requests withdrawal and reconsideration of the claims rejected under 35 U.S.C. § 103(a).

Claims 16-18 were rejected under 35 U.S.C. 103(a) as being unpatentable under Sharp et al, Temple et al, Li et al, Noren et al, and Atkinson et al as applied above and in furtherance of Okasinski. Applicants successfully transverse this rejection.

Sharp et al, Temple et al, Li et al, Noren et al, and Atkinson et al are discussed above. Okasinski does not remedy the deficiencies of Sharp et al, Temple et al, Li et al, Noren et al, and Atkinson et al. Okasinski discloses "an eukaryotic expression vector containing HSV DNA and regulatory elements, and sites for subcloning a DNA of interest. In addition, Okasinski discloses methods of producing a mammalian cell line having cells containing the expression vector." (Office Action page 10). There is no motivation in the cited references to combine the teachings of the references so as to arrive at the claimed invention. Okasinski does not, alone or in combination with the other cited references, teach, motivate, or suggest anything which makes

obvious to one of ordinary skill in the art a sequence with a total length less than 150 nucleotides and a portion of human tRNA structural gene sequence with no more than 20 3' flanking residues.

Claims 16-18 are dependent on claim 14. Claim 14 is a nucleotide vector comprising the nonobvious sequence of claim 1. Since claim 1 and claim 14 are nonobvious, claims 16-18 which include this nonobvious sequence are nonobvious. Therefore, Applicant respectfully requests withdrawal and reconsideration of the claims rejected under 35 U.S.C. § 103(a).

DOUBLE PATENTING REJECTION OF CLAIMS

Claims 1-27, 29-31, and 38-39 were rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S.

Common Ownership

Application Serial No. 10/022,127 and Patent 6,309,830 were, at the time the invention of Application Serial No. 10/022,127 was made, owned by Human Gene Therapy Research Institute.

A terminal disclaimer is enclosed herewith to obviate the double patenting rejection.

DOUBLE PATENTING REJECTION

Examiner rejected claim 28 under 35 U.S.C. § 101 as claiming the same invention as that of claim 24 of U.S. patent No. 6, 309, 830 as a double patenting rejection. Applicant cancels claim 28 rendering this rejection moot. This rejection should now be withdrawn.

CONCLUSION

Applicants submit that in light of the foregoing amendments and remarks the claims are in a condition for allowance. Reconsideration is respectfully requested.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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